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APPELLANTS' REPLY BRIEF UNDER 37 C.F.R. §41.41	Attorney Docket Confirmation No.	UCAL-161 DIV 7273
	First Named Inventor	S. Finkbeiner
	Application Number	09/922,483
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Filing Date	August 2, 2001
	Group Art Unit	1648
	Examiner Name	B.R. Campbell
	Title	*Antibodies specific for proteins having polyglutamine expansions*

Sir:

This Reply Brief is submitted in response to the Examiner's Answer dated June 19, 2006, for which a two-month period for response was given, making this Reply Brief due on or before August 19, 2006. Accordingly, this Reply Brief is timely filed.

The Commissioner is hereby authorized to charge deposit account number 50-0815 in the amount of $500.00 to cover the fee required under 37 C.F.R. §41.20(b)(3) for filing Appellants' Request for Oral Hearing. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§1.17, 41.41, and 41.47 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number UCAL-161 DIV.

In view of the remarks set forth below, reconsideration and allowance are respectfully requested.

I. REMARKS

Oral Hearing

Under 37 C.F.R.§41.47, if Appellant desires an Oral Hearing, appellant must file, in a separate paper, a written request for such hearing accompanied by the fee set forth in 37 C.F.R.§41.20(b)(3) within two months from the date of the Examiner's Answer.

Appellants provide herewith a Request for Oral Hearing.

Rejection of claims 10-13 and 28-30 under 35 U.S.C.§ 112, first paragraph

Claims 10-13 and 28-30 were rejected under 35 U.S.C.§ 112, first paragraph, as allegedly lacking enablement. In support of this rejection, the Office argued that there is "no correlation in the prior art or the instant specification which would indicate that a compound that interferes with the antibody binding to the polyglutamine expansion of Huntington [sic] would interfere with the binding of the polyglutamine expansion protein to the normal cellular target." Final Office Action, page 5.

Arguments rebutting the rejection of claims 10-13 and 28-30 have been made during prosecution, and in Appellant's Brief, filed April 15, 2005. As discussed in Appellant's Appeal Brief as filed on April 15, 2005, and in responses to Office Actions during the course of prosecution, the present invention provides ample description of how to use the claimed invention without undue experimentation; those skilled in the art would find it reasonable to use the instant method as claimed to identify agents that modulate binding between a polyglutamine expansion-containing protein and a cellular target of the protein; and he examiner has not established a reasonable basis to question the enablement provided for the claimed invention. Accordingly, the instant invention as claimed meets the enablement requirement of 35 U.S.C.§112, first paragraph..

The following remarks are made in response to the Examiner's Answer. To the extent that many of the comments made in the Examiner's Answer merely reiterate comments made in various Office Actions during prosecution, such comments are not specifically addressed herein, as they have been addressed during prosecution and in Appellant's Brief as filed on April 15, 2005.

Examiner's Answer

The Examiner's Answer maintained the rejection of claims 10-13 and 28-30 under 35 U.S.C.§ 112, first paragraph. Appellant notes that the Examiner's Answer stated that claims 10-13 are rejected; however, it is noted that claims 10-13 and claims 28-30 are pending and are appealed.

Comments regarding technical matters

The Examiner's Answer made various assertions that appear to be opinion and not founded in evidence or sound scientific reasoning.

1) The Examiner's Answer stated that the specification does not teach a method of screening agents that will interfere with the interaction of mutant huntingtin protein with the normal cellular target of the huntingtin protein. The Examiner's Answer stated: "**You cannot measure the interaction between a protein (huntingtin) and its cellular target if you do not know what the structure of the cellular target is.**" Examiner's Answer, page 5. This statement is simply not correct.

There are numerous examples in the scientific literature of studies measuring the interaction between a protein and its cellular target, where the structure of the cellular target was not known. Standard assays for measuring interaction between a protein and its cellular target (e.g., a receptor for the protein) involve radiolabelling the protein; and determining the extent of labeling of a cell that expresses a target (e.g., a receptor) for the protein. An example of this is the binding of relaxin to its cellular target, which has only recently been elucidated. Many studies were conducted to measure the interaction between relaxin and its cellular target, years before the cellular target was identified and characterized.

Furthermore, the results reported in Kaji et al. ((2001) *J. Biochem.* 129:577-583; "Kaji") do not support the assertion that "you cannot measure the interaction between a protein (huntingtin) and its cellular target if you do not know what the structure of the cellular target is." Kaji used monoclonal antibodies specific for monocytes chemoattractant protein-1 (MCP-1) to identify peptides that would inhibit binding of MCP-1 to a cellular target (the MCP-1 receptor). Kaji states that peptides were identified that were strongly and specifically recognized by the monoclonal antibodies, and that **binding of the peptides to THP-1 cells** (which respond to MCP-1) was competitively inhibited by MCP-1. Kaji, Abstract; page 579, bridging paragraphs, columns 1 and 2; and page 579, column 2, first full

paragraph. Thus, Kaji, using an assay involving binding of the identified peptides to THP-1 cells, and competitive inhibition of the peptide binding by MCP-1, was able to conclude that the peptides mimic the MCP-1 binding domain to the MCP-1 receptor. There was no need to have any knowledge whatsoever of the MCP-1 receptor. Although Kaji did know the identity of the cellular target of MCP-1, such was not necessary in order to conduct the cell-binding assay described on page 579, column 2, first full paragraph, of Kaji.

2) The Examiner's Answer stated: "**In order for an antibody to be considered a "surrogate receptor" it would have to bind the huntingtin protein at the same location that the undisclosed and unidentified cellular target binds the polyglutamine expansion of the huntingtin protein.**" Examiner's Answer, page 5.

As has been noted previously, the antibodies described in the instant specification recognize substantially the entire polyglutamine fold. An antibody is a protein. An antibody that recognizes conformational epitopes (as do the antibodies described in the instant specification) includes amino acid residues that make contact with the polyglutamine expansion. A cellular target would be expected to be a protein(s) that include amino acid residues that make contact with the polyglutamine expansion. As such, antibodies described in the instant specification are expected to serve as surrogates for a cellular target. Those skilled in the art would find it reasonable that antibodies described in the instant specification interact with a polyglutamine expansion in a manner similar to the manner in which a cellular target interacts with the polyglutamine expansion, e.g., amino acid side chains making contact with the polyglutamine expansion. As such, those skilled in the art would find it reasonable that compounds identified using a method as recited in the appealed claims will modulate interaction between a polyglutamine expansion-containing protein and a cellular target of that protein.

3) The Examiner's Answer stated: "A compound that interferes with the antibody binding to the polyglutamine expansion protein can act on the antibody alone or the compound can bind to the polyglutamine expansion protein." and "**Only those compounds that bind to the polyglutamine expansion protein may affect the binding of the protein to the cellular target.**" Examiner's Answer, page 5. First, this is not correct. Secondly, even if it were correct, such would not be a basis for establishing non-enablement of the instant claims.

The statement that "only those compounds that bind to the polyglutamine expansion protein may affect the binding of the protein to the cellular target" is not correct. Even if a test agent were to bind directly to an antibody, such would not preclude its usefulness as an agent that modulates interaction between a protein comprising a polyglutamine expansion and a cellular target of the protein.

For example, the results reported in Kaji do not support the assertion that "only those compounds that bind to the polyglutamine expansion protein may affect the binding of the protein to the cellular target." Kaji used monoclonal antibodies specific for monocytes chemoattractant protein-1 (MCP-1) to identify peptides that would inhibit binding of MCP-1 to a cellular target (the MCP-1 receptor). Kaji states that peptides were identified that were **strongly and specifically recognized** by the monoclonal antibodies, and that binding of the peptides to THP-1 cells (which respond to MCP-1) was competitively inhibited by MCP-1. Kaji, Abstract; page 579, bridging paragraphs, columns 1 and 2; and page 579, column 2, first full paragraph. Kaji thus discloses agents that bind to monoclonal antibodies to a protein and that modulate binding of the protein to its cellular target.

Secondly, even if it were true that "only those compounds that bind to the polyglutamine expansion protein may affect the binding of the protein to the cellular target," such would not be a basis for establishing a non-enablement rejection of the instant claims. The possibility that there may be some agents that are identified by a claimed method that do not modulate binding interaction of a polyglutamine expansion-containing protein and a cellular target of the protein, does not, under the law, support a conclusion that the claims lack enablement.

As the court has explained, even in unpredictable arts the specification does not have to disclose every species of a genus that would work and every species that would not work. The court has very clearly explained[1]:

> "To require such a complete disclosure would apparently necessitate a patent application or applications with thousands of catalysts....More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer

[1] *In re Angstadt*, 190 USPQ 214, at 219 (CCPA 1976)

could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used ...."

4) The Examiner's Answer stated that the Office has met its burden "by explaining that **neither Appellants specification nor the art in general has shown that the disclosed antibodies would inhibit the binding of the huntingtin protein (a polyglutamine expansion protein) to the cellular target**." Examiner's Answer, page 9.

However, as previously explained, it is not necessary to show that an antibody to a polyglutamine expansion-containing protein inhibits binding of the protein to a cellular target of the protein in order for the antibody to serve as a surrogate for a cellular target of the protein. It is not necessary to show that an antibody to a polyglutamine expansion-containing protein inhibits binding of the protein to a cellular target of the protein in order for the appealed claims to be enabled.

5) The Examiner's Answer stated that both the South and the Kaji references teach "**only those antibodies that inhibit the activity of the protein are able to function as "surrogate" receptor in screening assays**." Examiner's Answer, page 16. This is not correct.

Kaji used monoclonal antibodies specific for MCP-1 to identify peptides that would inhibit binding of MCP-1 to a cellular target (the MCP-1 receptor). Using the antibodies as a surrogate receptor, Kaji identified peptides that were strongly and specifically recognized by the monoclonal antibodies. The peptides were identified by screening a phage display library with monoclonal antibodies to MCP-1. Kaji then tested the binding activity of the identified peptides to THP-1 cells (which respond to MCP-1). Kaji found that binding of the peptides to THP-1 cells was competitively inhibited by MCP-1. Kaji, Abstract; page 579, bridging paragraphs, columns 1 and 2; and page 579, column 2, first full paragraph. Nowhere does Kaji teach, as the Examiner's Answer asserted, that "**only** those antibodies that inhibit the activity of the protein are able to function as "surrogate" receptor in screening assays."

The Examiner's Answer used this assertion to support its argument that "[b]ecause the cellular receptor for huntingtin protein is not known the ordinary artisan cannot test if the disclosed antibodies

actually inhibit the binding of the huntingtin protein to its cellular target." Examiner's Answer, page 16. However, as noted above, demonstration that the antibody inhibits the binding of the huntingtin protein to its cellular target is not a requirement in order for the methods to function as claimed.

6) The Examiner's Answer cited a statement in Appellant's Appeal Brief that the "antibodies in the claimed method do not serve to prevent the binding of the polyglutamine expansion-containing protein to its cellular target." Examiner's Answer, page 15. The Examiner's Answer concluded that "by Appellants own admission the antibodies of the instant invention cannot serve as a "surrogate cellular target" because the antibodies do not prevent the binding of the polyglutamine repeat containing protein (huntingtin) to the cellular target." Examiner's Answer, page 15. This is not correct.

The cited statement in Appellant's Appeal Brief has been misconstrued. The statement says that *in the claimed method*, the antibodies are not serving the purpose of preventing binding of the polyglutamine expansion-containing protein to its cellular target. Clearly, *in the claimed method*, the antibody serves as a surrogate for a cellular target of the polyglutamine expansion-containing protein. Appellant has made no admission that an antibody as described in the instant specification would not be capable of inhibiting binding of a polyglutamine repeat containing protein to a cellular target of the protein. Appellant merely noted that that is not the role that the antibody serves in the claimed method.

Comments regarding the art

The Examiner's Answer discussed: a) Heiser et al. ((2000) *Proc. Natl. Acad. Sci. USA* 97:6739-6744; "Heiser"); b) South et al. ((1995) *Thromb. Haemost.* 73:144-150; "South"); and c) Kaji.

Heiser

The Examiner's Answer appears to reiterate previous remarks regarding Heiser. The Examiner's Answer stated that neither the Heiser reference nor any other reference in the prior art provide any information regarding the normal cellular target for the huntingtin protein. However, as discussed previously, Heiser is not relevant to a determination as to whether the appealed claims are enabled.

No conclusion as to the enablement of the instant claims can be drawn from the disclosure of Heiser. As the May 20, 2003 Office Action acknowledged, Heiser examined interference with self aggregation of huntingtin. Heiser does not disclose agents that inhibit a binding interaction between an

antibody to a polyglutamine expansion of a polyglutamine expansion-containing protein; and does not comment on the relevance of same to the identification of agents that modulate binding interaction between a polyglutamine expansion-containing protein and a cellular target of the protein.

South

The Examiner's Answer appears to reiterate previous remarks regarding South. The Examiner's Answer stated that the critical difference between South and the instant specification in that the authors of South knew that the antibody binds to the vWF protein at a region that is required for the binding of the vWRF protein to the GPIb receptor. However, this alleged "critical difference" is irrelevant to a determination as to whether the appealed claims are enabled.

South successfully used antibody binding to a domain of vWF as a surrogate, or a model, for vWF-GPIb binding; and, using the monoclonal antibodies, successfully identified peptides that inhibited vWF-GPIb binding. In a manner analogous to South, the instant claims use antibody specific for a polyglutamine expansion of a polyglutamine expansion-containing protein to identify agents that modulate the binding interaction between the polyglutamine expansion-containing protein and its cellular target.

The Examiner's Answer stated: "In the instant specification the antibody binds to the polyglutamine expansion protein, yet there is no correlation provided that this region is the same region that is responsible for the binding [of] the polyglutamine expansion protein to the normal cellular target." Examiner's Answer, page 6.

First, given the number of intracellular abnormalities that have been described, mutant huntingtin may not act on a single target. Instead, it is possible that the structure, which disease-associated polyglutamine expansions adopt and which is recognized by an antibody as described in the instant specification, enables mutant huntingtin to interact with multiple intracellular targets, leading to neurodegeneration. Such a possibility is supported by the numerous proteins that have been identified as interacting with mutant huntingtin using proteomic or interaction-trap approaches. As such, an assay focused on disrupting interactions of proteins with a common secondary structure formed by disease-associated polyglutamine expansions has the potential for protecting multiple intracellular targets within neurons against the deleterious actions of mutant huntingtin. As an example, the monoclonal antibody

referred to as 3B5H10 in the instant specification recognizes such a structure and is thus useful for identifying compounds that modulate interaction between huntingtin and a cellular target of huntingtin. It is expected that at least some of the compounds identified will be neuroprotective.

Second, the crystal structure of the polyglutamine binding moiety of mAb 3B5H10 has been solved; and additional small angle X-ray scattering data on the co-complex formed between mutant huntingtin and the binding moiety of 3B5H10 have been generated. Importantly, these data support the view that the antibody binds to a parallel or antiparallel beta-sheet structure formed by a monomer of mutant huntingtin. The current model suggests that the binding site appears to span a 14-residue edge of polyglutamines, with additional interactions between the beta sheet formed by polyglutamines (i.e., the second strand of polyglutamines) and a unique beta sheet formed by the third complentarity determining region (CDR) of the antibody's light chain. In other words, the epitope bound by the antibody is nearly the entire disease-associated polyglutamine expansion and therefore is ideal for small molecule screening.

Finally, although there are as yet no direct data on the structure of intracellular protein targets bound by mutant huntingtin, an automated microscope has been used in conjunction with mAb 3B5H10 to elucidate the biological significance of the structure to which it binds. It has been found that binding by 3B5H10 to huntingtin predicts the timing and amount of degeneration in a striatal neuron model of Huntington's Disease. In short, binding by 3B5H10 is a predictor of neurodegeneration.

In recent studies relating the interaction between antibodies described in the instant specification and a polyglutamine expansion, a database of proteins whose structures have been solved was reviewed, and proteins that bind glutamines were analyzed. It was found that the amino acids that make contact with the glutamine in many such proteins have aromatic side chains, e.g, phenylalanine, tryptophan, etc. Structural studies of the 3B5H10 antibody show that this antibody has key tryptophan residues located at sites that are believed to mediate binding to mutant huntingtin, together with the beta-sheet structure formed by one of the CDRs.

Nagai et al. ((April 7, 2000) *J. Biol. Chem.* 275:10437-10442; "Nagai") describes screening a phage display peptide library for binding to a polyglutamine expansion. Nagai found that peptides that bind to polyglutamine expansions are rich in tryptophan residues. At least one of the peptides inhibited

polyglutamine induced cell death. Nagai provides a structure-based model for how polyglutamine expansions could bind tightly and selectively to specific intracellular targets. As such, antibodies to polyglutamine expansions as described in the instant specification serve as valuable surrogates for a variety of such interactions and as a tool to carry out methods as claimed to identify small molecules to disrupt such interactions, even in the absence of specific information about the identity of intracellular target(s) for polyglutamine expansion-containing proteins such as huntingtin.

Kaji

The Examiner's Answer appears to reiterate previous remarks regarding Kaji. The Examiner's Answer stated that the critical difference between Kaji and the instant specification is that in Kaji the authors have associated an activity that is inhibited with the antibody. However, this alleged "critical difference" is irrelevant to a determination as to whether the appealed claims are enabled.

Kaji successfully used antibody binding to a domain on the MCP-1 protein as a surrogate, or a model, for the binding of the MCP-1 protein to its cellular target, i.e., the MCP-1 receptor. Using the antibody as a surrogate for the MCP-1 receptor, Kaji found peptides that bound the antibody, and that also bound the MCP-1 receptor. In a manner analogous to Kaji, the instant claims use antibody specific for a polyglutamine expansion of a polyglutamine expansion-containing protein to identify agents that modulate the binding interaction between the polyglutamine expansion-containing protein and its cellular target.

Comments regarding the Stein Declaration

The Examiner's Answer stated that the Declaration of Ross Stein ("the Stein Declaration") does not overcome the rejection "because the declaration does not actually indicate that the antibody binds to the polyglutamine expansion in the same location where the cellular target binds to the polyglutamine expansion." Examiner's Answer, page 8. However, this is insufficient reason to dismiss the Stein Declaration.

Appellant's arguments, and the Stein Declaration, have been made of record. As noted previously, Dr. Stein is an expert in the field of enzyme kinetics and drug discovery. The Stein Declaration stated that it is reasonable to use an assay as claimed to identify agents that inhibit binding of a protein containing a polyglutamine expansion to its cellular target, and that such an assay represents

an important and valuable approach to identifying new therapeutic agents for neurodegenerative diseases. The Stein Declaration stated that a grant application describing the screening approach was reviewed by a panel, and indicated that the panel was in support of this approach. Indeed, the grant eventually received a 1.4% priority score, meaning that it scored better than 98.6% of other grant. Thus, those skilled in the art would find it convincing that the instant specification is enabling for the claimed invention.

Furthermore, a collaboration between the Appellant's laboratory and the laboratory of Dr. Ross Stein, Director of the Laboratory for Drug Discovery in Neurodegeneration at the Harvard Center for Neurodegeneration and Repair, in which an assay as recited in the appealed claims was used, has yielded a number of compounds that inhibit binding between an antibody as recited in the claims and mutant huntintin protein that comprises a polyglutamine expansion (mHtt). These compounds are being tested for their ability to affect survival of neurons transfected with a construct encoding mHtt.

Appellant notes that, while the examiner has attempted to cast doubt on the enablement of the claimed methods, those skilled in the art of drug discovery, including the many reviewers of the above-mentioned grant application, considered it reasonable that the methods as claimed provide for identification of agents that modulate binding interaction between a polyglutamine expansion-containing protein and a cellular target of the protein.

Appellant's specification has taught how to make and use the claimed invention such that those of ordinary skill in the art can practice the claimed invention. As such, Appellant respectfully requests that the rejection of claims 10-13 and 28-30 under 35 U.S.C.§112, first paragraph, be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Conclusion as to the rejection under 35 U.S.C.§112, first paragraph

The present invention provides ample description of how to use the claimed invention without undue experimentation. Those skilled in the art would find it reasonable to use the instant method as claimed to identify agents that modulate binding between a polyglutamine expansion-containing protein and a cellular target of the protein. The examiner has not established a reasonable basis to question the enablement provided for the claimed invention. Accordingly, the instant invention as claimed meets the

enablement requirement of 35 U.S.C.§112, first paragraph.

II. CONCLUSION

Appellants present further arguments that the appealed claims meet the enablement requirement of 35 U.S.C.§112, first paragraph. Additional arguments have already been presented, both in responses to Office Actions during the course of prosecution, as well as in Appellant's Brief. In view of the remarks set forth above, and those already of record, Appellants respectfully request that the rejection of claims 10-13 be withdrawn, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL-161 DIV.

Respectfully submitted,
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Date: Aug. 18, 2006

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